## Remarks/Arguments

Reconsideration of this application, as amended, is respectfully requested.

### I. Status of the Claims

After entry of these amendments, claims 1-32 are pending. Claim 1 is amended at the request of the Examiner, to recite that "the NH is linked to a carbon ortho to a nitrogen on the HetAr ring." Claims 33-46 are canceled without prejudice, as covering a non-elected invention.

### II. Restriction Requirement

In the amendment filed September 22, 2008, applicants elected the Group I claims, claims 1-32, covering 3-fluoropiperidine compounds (including pharmaceutical composition claim 32), with traverse. The Examiner denied applicants' traversal. In response, non-elected claims 33-46 are canceled (without prejudice) as covering a non-elected invention.

The Examiner also concludes that "[t]he claims are examined to the extent that they read on the compounds wherein the NH shown in the formula (I) linked to the carbon ortho to the nitrogen on the HetAr ring." In response, the claims are amended to be consistent with the scope of examination.

The Examiner is reminded of the rejoinder provisions of M.P.E.P. § 821.04, which provides for rejoinder of process claims which are dependent from or include all the limitations of an allowable product claim. Further, the PCT administrative instructions on Unity of Invention state that for claims to a product, unity of invention permits inclusion of "an independent claim for the use of said product." See M.P.E.P., Annex B, Unity of Invention, Sect. (e)(i).

Thus, applicants should be permitted to rejoin a method of use claim upon a determination of allowability of the pending claims 1-32.

### III. Anticipation and Obviousness Rejections

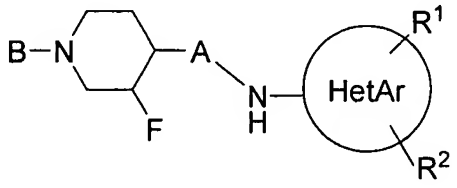
Claims 1-32 stand rejected under 35 U.S.C. § 102(b) or in the alternative, under 35 U.S.C. § 103(a) as obvious over WO 02/068409. In support of the anticipation rejection, the Examiner states that formula (I) of claim 1 of WO '409 "includes compounds of the instant formula (I)" when X is F. In support of the obviousness rejection, the Examiner states that "[t]he difference between the prior art and instant claims is that, in the prior art, the disclosed specific compounds are limited to piperidine unsubstituted at the 3-position." The Examiner acknowledges that 3-fluoropiperidines are not claimed but are "generically taught" in WO '409. The Examiner states that "one skilled in the art of medicinal chemistry, because of the known similarity of F and H in size, would be motivated to make 3-fluoropiperidine compounds as alternate forms of the piperidine compounds of [WO '409] as NMDA antagonists."

Applicants do not dispute that the broad generic description in WO '409 encompasses the compounds claimed in this application. However, as explained below, the claimed compounds are neither anticipated by nor obvious over the disclosure of WO '409.

**A. Response to Anticipation Rejection**

Applicants respectfully traverse the anticipation rejection, on the grounds that the claimed compounds are not described in WO '409. "Anticipation" means that the claimed subject matter is not new, but was previously known. *See e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Anticipation of a claimed invention requires that "each and every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention." *Sanofi* at 1082. Further, the anticipatory reference "'must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.'" *Sanofi* at 1083 (quoting *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586, 587 (1972)).

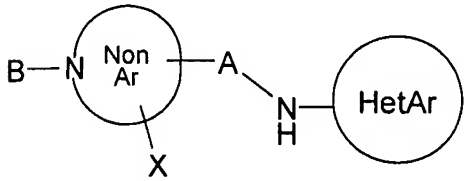
Here, all of the limitations of the claimed compounds are not "clearly and unequivocally" described in WO '409. The claims require compounds having the formula (I):




(I)

or a pharmaceutically acceptable salt thereof, wherein a fluoro group is fixed at position-3 of a piperidine ring.

The limitation of fluoro substitution at the 3-position of a piperidine ring is not found in WO '409. Rather, WO '409 describes a broad group of possible X substituents present on a non-aromatic nitrogen-containing ring, as shown below:

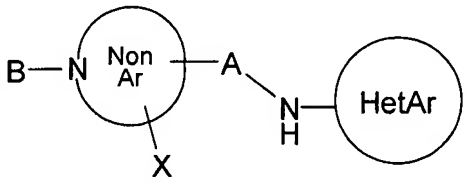


At page 5, lines 4-5, X is defined as any one of hydrogen, hydroxy, fluoro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $NH_2$ or =O. The specific 3-fluoro piperidine limitation of the claims is not disclosed in any of the compounds of WO '409. Only Example 147 of WO '409 has a fluoro substituent on the nitrogen-containing core ring (piperidine). However, the fluoro substituent of Example 147 is present at the 4-position of the piperidine, rather than the 3-position as required by the claims of this application. Since none of the compounds of WO '409 have the specific limitations of the claimed compounds, the claims are not anticipated.

Hence, the claimed compounds are not anticipated by WO '409.

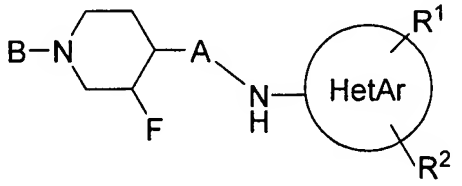
**B. <u>Response to Obviousness Rejection</u>**

Applicants also traverse the Examiner's obviousness rejection, on the grounds that all pending claims are not suggested by the teachings of WO 02/068409. WO '409 describes a broad group of possible X substituents present on a non-aromatic nitrogen-containing ring, as shown below:




At page 5, lines 4-5, X is defined as any one of hydrogen, hydroxy, fluoro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $NH_2$ or =O. At page 3, lines 20-21, "NonAr" is defined as "a nonaromatic 5-7 membered ring containing 1 or 2 nitrogen ring atoms or an aza bicyclo octane ring."

In contrast, the claims of this application require that X is a fluoro substituent present at the 3-position of a piperidine ring, as shown below:




The specific structural requirements of the claimed compounds (fluoro substitution at the 3-position of the piperidine ring) is not suggested by WO '409. In fact, in order to arrive at the claimed compounds from the general teachings of WO '409, one would need to

(1) select piperidine from the possible "NonAr" groups;
(2) select fluoro from the various X groups; and
(3) fix the X substitution at the 3-position of the piperidine ring.

There is no reasonable suggestion to do this in WO '409. WO '409 does not identify fluoro as a preferred X group. In fact, the vast majority of the 187 exemplified compounds in WO '409 have an unsubstituted non-aromatic nitrogen containing ring, where X is in effect hydrogen. The only substituted compounds are Examples 39-43, 54 and 147. Of these, only Example 147 has a fluoro substituent. The fluoro substituent of Example 147 is present at the 4-position of the piperidine (rather than the 3-position as required by the claims of this application). Examples 39-43 each have a hydroxy substituent at the 3-position, and Example 54 has hydroxy substitution at the 4-position.

In support of the obviousness rejection, the Examiner states that "one skilled in the art of medicinal chemistry, because of the known similarity of F and H in size, would be motivated to make 3-fluoropiperidine compounds as alternate forms of the piperidine compounds of [WO '409] as NMDA antagonists." However, the prior art lacks any suggestion of the claimed compounds.

Even if there is prima facie obviousness, applicants submit evidence of the unexpectedly superior properties of the claimed compounds, thereby rebutting the obviousness claim. The accompanying Declarations of Joseph J. Lynch and Rodney A. Bednar contain comparative data, demonstrating the unexpectedly improved properties of the claimed compounds over the compounds disclosed in WO '409.

The Bednar Declaration compares the in vitro binding affinity (Ki) of Examples 1, 2, 5, 6 and 7 of the present application against Examples 8, 39, 40 and 171 from WO '409. The Ki values for the instant examples have, unpredictably, been found to be significantly lower than those of the most structurally similar compounds exemplified in WO '409. For instance, Example 1 of this application is more than fifteen times more active than Example 39 of WO '409, and Example 6 of this application is nearly five times more active than Example 8 of WO '409. The binding assay is described beginning at page 10 of the specification.

The Lynch Declaration compares the *in vivo* potency of the present invention's Example 1 compound to a structurally similar compound Example 17 of WO '409. Here, Example 1 shows a seven-fold improvement in potency when administered intravenously, as compared to prior art Example 17.

In view of this data, the compounds of the present invention show an unexpected improvement in pharmaceutical activity relative to structurally similar compounds of WO '409. There is no teaching within the disclosure of WO '409 which would lead one skilled in the art to select or identify these unexpectedly advantageous compounds. The claimed invention is therefore non-obvious over the prior art.

## IV. Conclusion

In view of the action taken, it is believed that claims are neither anticipated by nor obvious over WO '409. It is respectfully requested that the rejections be withdrawn.

Respectfully submitted,

By _____

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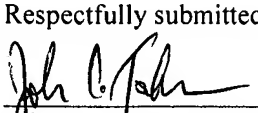
## IV. Conclusion

In view of the action taken, it is believed that claims are neither anticipated by nor obvious over WO '409. It is respectfully requested that the rejections be withdrawn.

Respectfully submitted,

By 

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